

Synthesis of *meso*-2,2'-bipyridyl-substituted calix[4]arenes and their response to metal cations

T. D. Moseev^a, A. F. Khasanov^{ab}, M. V. Varaksin^{ab},
D. S. Kopchuk^{ab}, I. S. Kovalev^a, O. S. Taniya^{ab},
M. Rahman^a, S. Santra^a, G. V. Zyryanov^{ab*},
O. N. Chupakhin^{ab}, V. N. Charushin^{ab}

^a Ural Federal University named after the first President of Russia B. N. Yeltsin,
19 Mira st., Ekaterinburg, 620002, Russian Federation

^b I. Ya. Postovsky Institute of Organic Synthesis of RAS (Ural Branch),
22/20 S. Kovalevskoy/Akademicheskaya st., Ekaterinburg, 620990, Russian
Federation

*email: g.v.zyryanov@urfu.ru

Abstract. A convenient synthetic approach to *meso*-substituted with 2,2'-bipyridine and 1-(pyridin-2-yl)isoquinoline residues calix[4]arenes is reported. This approach involves the reaction of generated *in situ* 2-lithio-calix[4]arene with 1,2,4-triazine precursor with the following aromatization of the obtained adduct, and the *aza*-Diels-Alder reaction of the 1,2,4-triazinyl-substituted calix[4]arene with 2,5-norbornadien or *in-situ* generated 1,2-dehydrobenzene. The UV/fluorescence response of thus obtained *meso*-pyridyl-substituted calix[4]arenes to metal cations is studied.

Keywords: calix[4]arene; 1,2,4-triazines; *aza*-Diels-Alder reaction; 2,2'-bipyridines; visual cations detection

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Introduction

Calix[4]arenes and their derivatives are, probably, the mostly studied supramolecular hosts for various applications for analytical chemistry [1], materials science [2], as well as environmental [3] and medicinal [4] applications. By means the proper synthetic modification various calixarene derivatives bearing extra heterocyclic ligand units or other receptor units

at the upper or lower rim were obtained to be used for the recognition/supramolecular extraction of inorganic [5] and organic cations [6], anions [7], as well as some neutral molecules [8]. In this article we wish to report a method for the preparation of *meso*-2,2'-bipyridyl-substituted calix[4]arenes and their response to metal cations.

Experimental part

¹H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz), the internal standard was SiMe₄. Mass-spectra (ionization

type — electrospray) were recorded on a MicroTOF-Q II instrument from Bruker Daltonics (Bremen, Germany). Elemental analysis was performed on a Perkin Elmer

PE 2400 II CHN analyzer. Fluorescence spectra were measured on Horiba Fluoromax-4 spectrofluorometer. Absolute quantum yields were measured by using the integrating sphere. UV-spectra were measured on Shimadzu UV-1800 spectrometer. The starting *meso*-triazinyl-substituted calix[4]arenes were prepared as reported [9].

Meso-2,2'-bipyridyl-substituted calix[4]arene (3). In a 50 ml round-bottom flask to a solution of 2-(6-phenyl-3-(2-pyridyl)-1,2,4-triazin-5-yl)-25,26,27,28-tetramethoxycalix[4]arene **2** (0.106 g, 0.15 mmol) in 10 ml of *o*-xylene 2,5-norbornadiene (0.15 ml) was added and the resulting solution was heated at a temperature of 130–150 °C for 12 hours under the argon atmosphere. Then another 0.1 ml of 2,5-norbornadiene were added and the reaction mixture was heated for another 6 hours at a temperature of 130–150 °C. *o*-Xylene was distilled off under reduced pressure, and the column chromatography (eluent — ethyl acetate) resulted in the product **3** (*R*_f = 0.55). Yield 69 mg (0.097 mmol, 65%), mp >250°C. NMR ¹H (CDCl₃, δ, ppm): 8.64 (1H, d, *J*=4.9 Hz, H-6 (2-Py)), 8.43–8.51 (1H, dd, *J*=8.2 Hz, *J*=15.1 Hz, H-3 (Py)), 8.33–8.37 (1H, dd, *J*=2.7 Hz, *J*=8.2 Hz, H-4 (Py)), 7.67–7.76 (2H, m, H-3 (2-Py)), H-4 (2-Py)), 7.35–7.43 (2H, m, H-5 (2-Py), Ph), 7.27–7.33 (2H, m, Ph) 7.11–7.27 (5H, m, Ph), 6.90–6.97 (2H, m, Ph), 6.80–6.86 (2H, m, Ph), 6.67–6.77 (6H, m, Ph), 6.28, 5.70 (1H, s, C(2)H), 4.25–4.32, 4.12–4.17 (2H, m, Ar-CH₂Ar), 3.72–3.77 (4H, m, 1H ArCH₂Ar + 3H OMe), 3.65 (3H, s, OMe), 3.57 (1H, m, ArCH₂Ar), 3.42–3.48 (4H, m, 1H ArCH₂Ar + 3H OMe), 3.16 (3H, m, 3H OMe), 2.85 (1H, m, ArCH₂Ar). Found: C 81.27%, H 6.15%. C₄₈H₄₂N₂O₄. Calculated: C 81.10%, H 5.96%.

Meso-1-(pyridin-2-yl)isoquinolinyl-substituted calix[4]arene (4). In a 100 ml three-necked flask equipped with a reflux condense 2-(6-phenyl-3-(pyridin-2-yl)-1,2,4-triazin-5-yl)-25,26,27,28-tetramethoxycalix[4]arene (0.142 g, 0.2 mmol) was dissolved and 0.1 ml of *iso*-amyl nitrite (0.7 mmol) in 40 ml of dry toluene was added at once. Under argon atmosphere the resulted solution was heated to a temperature of 105–110 °C, and a solution of anthranilic acid (96 mg, 0.7 mmol) in 20 ml of 1,4-dioxane was added to dropwise for 30 minutes with an intensive stirring the reaction mixture. After that the reaction was kept under such conditions for 60 minutes. The reaction mixture was than cooled down to room temperature and washed with a 30% aqueous alkali solution (4 times 50 ml each), the organic phase was separated, dried with an anhydrous sodium sulfate, filtered and the solvent was distilled off under reduced pressure. The product **4** was isolated by column chromatography (dichloromethane: ethyl acetate in a ratio of 4: 1, *R*_f = 0.85). Yield 10 mg (0.012 mmol, 6.0%), mp >250°C. NMR ¹H (CDCl₃, δ, ppm): 8.89 (1H, d, *J*=4.9 Hz, H-6 (2-Py)), 8.41–8.48 (1H, dd, *J*=8.2 Hz, *J*=15.1 Hz, H-3 (2-Py)), 8.79–8.88 (1H, dd, *J*=2.7 Hz, *J*=8.2 Hz, H-4 (2-Py)), 7.59–7.66 (2H, m, H-5 (2-Py), Ph), 7.46–7.55 (4H, m, Ph), 7.39–7.46 (3H, m, Ph), 7.08–7.18 (2H, m, Ph), 6.89–7.04 (2H, m, Ph), 6.83–6.88 (2H, m, Ph), 6.65–6.76 (5H, m, Ph), 6.57–6.64 (2H, m, Ph), 6.35, 5.96 (1H, s, C(2)H), 4.25–4.32, 4.12–4.17 (2H, m, Ar-CH₂Ar), 3.72–3.77 (4H, m, 1H ArCH₂Ar + 3H OMe), 3.65 (3H, s, OMe), 3.57 (1H, m, ArCH₂Ar), 3.42–3.48 (4H, m, 1H ArCH₂Ar + 3H OMe), 3.16 (3H, m, 3H OMe), 2.85 (1H, m, ArCH₂Ar). Found: C 81.91%, H 5.77%. C₅₂H₄₄N₂O₄. Calculated: : C 82.08%, H 5.83%.

Studies of the interactions of calixarenes 3–4 with cations

The studies of the interactions of compounds 3–4 with Zn^{2+} and Cd^{2+} cations were carried out at the concentrations

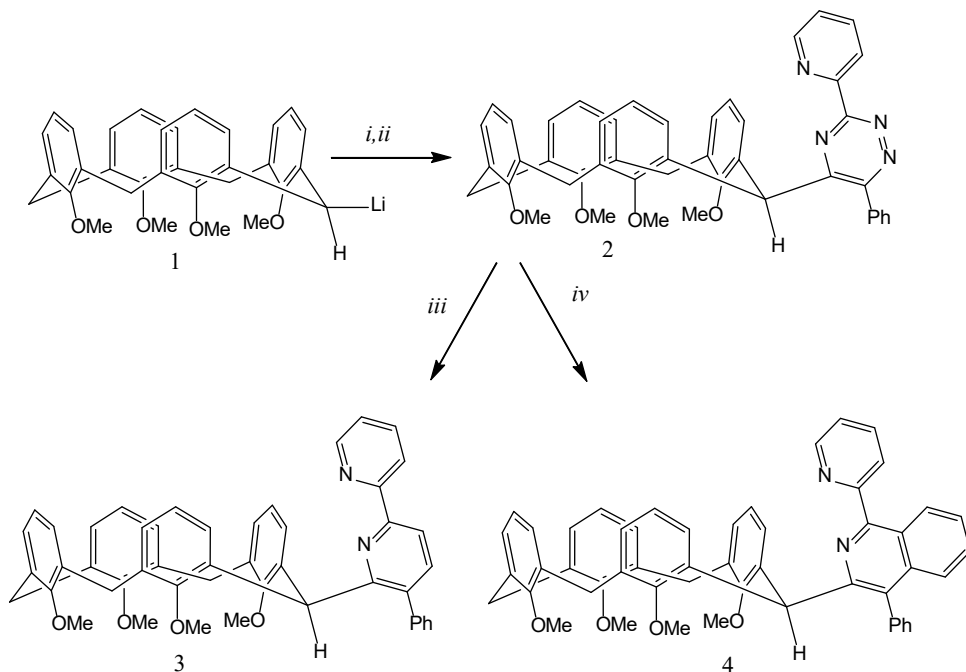
of 3–4 of $(1-9) \cdot 10^{-6}$ M (depending on the value of the absorption coefficient ($A \leq 0.1$)) in anhydrous freshly distilled THF. The concentrations of cations were 10^{-3} – 10^{-4} M.

Results and discussion

A most common method for the introducing of (bi)pyridine moieties into the calix[4]arenes is the modification of upper or lower ring the calixarene core with oligopyridine-attached spacer groups by means of acylation, alkylation or condensation reactions [9–17]. As an alternative approach our group reported the direct modification of an upper ring of calix[4]arene moiety with 3-(2-pyridyl)-1,2,4-triazine-5(2*H*) — one residues [18]. For these modified calixarenes an effectiveness for their transport of La^{3+} cations

was confirmed. Additionally, we reported recently an effective synthetic approach to *meso*-substituted with 1,2,4-triazine moieties calix[4]arenes *via* direct modification of 5-H-1,2,4-triazines by the reaction with generated *in situ* 2-lithio-calix[4]arene and the following aromatization [9] (Scheme 1).

From another hand the 1,2,4-triazines are suitable precursors for the preparation of multi-substituted (bi)pyridine ligands/fluorophores *via* the inverse demand Diels-Alder/retro-Diels-Alder reaction sequence



Scheme 1. Reagents and conditions: *i*) 1.6 M *n*-BuLi, TMEDA, THF, -78°C , 1h, then 25°C overnight; *ii*) DDQ (1.2 eq.), THF, 25°C , 0.5 h; *iii*) 2,5-norbornadiene, *o*-xylene, 130 – 150°C , 18 h; *iv*) anthranilic acid, *iso*-amylnitrite, 1,4-dioxane-toluene, 105 – 110°C , 1.5 h.

with various dienophiles, such as 2,5-norbornadiene [20], enamines [21], acetylene equivalents [22] or arylene intermediates [23].

Keeping in mind all the mentioned above we decided to prepare new calix[4]arenes *meso*-substituted with (benzo)pyridine moieties and study their response to selected metal cations. To do that as a first step we prepared the corresponding *meso*-1,2,4-triazine-substituted calixarene **2** using the previously reported procedure [9]. As a next step the ID Diels-Alder reaction between **2** and 2,5-norbornadiene was carried out to afford smoothly *meso*-2,2'-bipyridyl-substituted calix[4]arene **3** in up to 65% yield (Scheme 1). The photophysical properties of calixarene **3** are presented below (Table 1).

The introduction of bipyridyl ligand/fluorophore on the periphery of calix[4]arene caused the change in the photophysical properties of product **3**. Thus, in THF

solution calixarene **3** has a strong absorbance band near 292 nm and an emission peak near 379 nm. Calculated absolute fluorescence quantum yield was 1.1%.

The response of calixarene **3** to Zn^{2+} and Cd^{2+} cations is shown below. Thus, in UV-spectra the addition of 1 eq. of these cations caused a strong decrease of the absorbance peak at 292 nm (Fig. 1).

The same trend was observed in the emission spectra. Thus, upon addition of 1 eq. of Cd^{2+} or Zn^{2+} a dramatic fluorescence quenching was observed along with the bathochromic shift of the emission maxima by 5–20 nm. It worth to mention that, the addition of Zn^{2+} caused the stronger red-shift, while the addition of Cd^{2+} caused stronger fluorescence quenching (Fig. 2).

As a last step the isoquinoline-substituted calixarene **4** was obtained by using the reaction between **2** and benzyne generated *in situ* as reported before [23]. The re-

Table 1

Photophysical properties of calixarene 3(C3) in THF solution

#	$\lambda_{\text{abs max}}^{\text{a}}$, nm	$\lambda_{\text{em max}}^{\text{b}}$, nm	$\epsilon_{\text{M}}^{\text{c}}$ (at $\lambda_{\text{abs max}}$, $10^4 \text{ M}^{-1} \cdot \text{cm}^{-1}$)	Stokes shift, nm	$\Phi_{\text{p}} (\%)^{\text{c}}$ (λ_{ex} , nm) ^d
C3	292	379	1.60	113	1.1 (292 nm)

^a absorption maxima in THF at room temperature; ^b fluorescence maxima in THF at room temperature; ^c absolute photoluminescence quantum yield in THF; ^d excitation wavelength

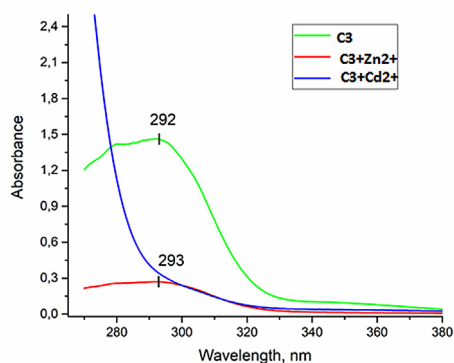


Fig. 1. UV-spectra of calixarene **3** in the presence of Cd^{2+} and Zn^{2+}

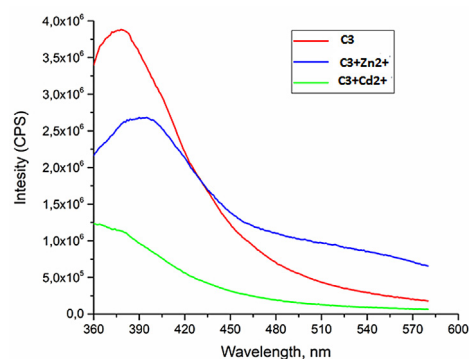


Fig. 2. Emission spectra of calixarene **3** in the presence of Cd^{2+} and Zn^{2+}

action afforded as low as 6% of the desired calixarene **4**, while the rest of the reaction mixture contains several non-identified products. In preliminary experiments in a solution of THF in the presence of even trace amounts of Cd^{2+} calixarene **4** exhibited a dramatic fluorescence quench-

ing. However, a lesser response to Zn^{2+} was observed. In our opinion, these results confirm the influence of a nature of pyridine substituents in the *meso*-position of the calix[4]arene core on the fluorescence response of whole calixarene molecule to the selected metal cations.

Conclusions

In summary, *meso*-pyridyl- and *meso*-isoquinoliny-substituted calix[4]arene ligands/fluorophores were prepared and their photophysical and coordination

properties to metal cations were studied. For the obtained *meso*-pyridyl-calixarenes strong fluorescence turn-off response towards Zn^{2+} and Cd^{2+} cations was observed.

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